CLAIMS

We claim:

1. A process for separating the R(-)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer [R(-)-I] or S(+)-[2-[[2-(2-ethoxyphenoxy)ethyl] amino]propyl]-2-methoxybenzenesulfonamide enantiomer [S(+)-I] from a mixture of said R(-)-I and S(+)-I enantiomers, comprising:

(a) placing a mixture containing the R(-)-I and S(+)-I enantiomers in contact, in a solvent, with an optically active organic acid to form diastereoisomeric salts with said R(-)-I and S(+)-I enantiomers, wherein said diastereoisomeric salts have different solubility in said solvent and can be separated by crystallization;

(b) separating the diastereoisomeric salt mixture enriched in the diastereoisomeric salt of the R(-)-I or S(+)-I enantiomer formed in step (a); and

(c) releasing the diastereoisomeric salt mixture separated in step (b) to obtain the R(-)-I or S(+)-I enantiomer or a mixture enriched in one of them.

2. Process according to claim 1, wherein prior to carrying out step (c), the diastereoisomeric salt mixture enriched in the diastereoisomeric salt of the R(-)-I or S(+)-I enantiomer separated in step (b) is resuspended or recrystallized, one time or more.

3. Process according to claim 1, wherein said mixture containing the R(-)-I and S(+)-I enantiomers is a racemic mixture.

4. Process according to claim 1, wherein said optically active organic acid capable of forming diastereoisomeric salts with said R(-)-I and S(+)-I enantiomers is selected among D-10-camphorsulfonic acid, L-10-camphorsulfonic acid, (-)-N-(3,5-dinitrobenzoyl)-α-phenyl-glycine acid and (+)-N-(3,5-dinitrobenzoyl)-α-phenylglycine acid.

5. Process according to claim 1, wherein said solvent is selected from the group formed by water, alcohols, ketones, nitriles and their mixtures.

6. Process according to claim 5, wherein said solvent is a mixture of acetone and water.

7. Process according to claim 1, wherein said diastereoisomeric salts are formed at a temperature comprised between 15°C and the reflux temperature of the solvent.

8. Process according to claim 1, wherein the separation of the diastereoisomeric salt mixture enriched in the R(-)-I or S(+)-I enantiomer is carried out by crystallization and separation of the crystals formed.

9. Process according to claim 1, wherein the separation of the diastereoisomeric salt mixture enriched in the R(-)-I or S(+)-I enantiomer comprises carrying out one or more recrystallizations or resuspensions of said diastereoisomeric salt mixture.

10. Process according to claim 1, wherein the release of the diastereoisomeric salt mixture enriched in one of the R(-)-I or S(+)-I enantiomers separated in step (b) is carried out by means of reaction with a base.

11. Process according to claim 1, wherein the separated enantiomer is the R(-)-I enantiomer.

12. Process according to claim 1, wherein the optically active organic acid used is selected among L-10-camphorsulfonic acid and (-)-N-(3,5-dinitrobenzoyl)-α-phenylglycine acid.

13. Process according to claim 1 for the separation of the R(-)-I enantiomer, comprising:

placing a mixture of R(-)-I and S(+)-I enantiomers in contact with L-10-camphorsulfonic acid [C(-)], to form the I(+)C(-) and I(-)C(-) diastereoisomeric salts, in a solvent in which mainly the I(-)C(-) salt precipitates over the I(+)C(-) salt;
separating the precipitate comprising mainly I(-)C(-) diastereoisomeric salt over the I(+)C(-) salt and resuspending it in a solvent;
maintaining the resulting suspension at a temperature comprised between 15°C and the reflux temperature of the solvent, for a time period comprised between 20 and 24 hours, to obtain a second precipitate mainly comprising the I(-)C(-) salt; and if so desired,

- neutralizing said second precipitate to mainly obtain the R(-)-I enantiomer, or
- resuspending said second precipitate, one time or more, in a solvent, to obtain the R(-)-I enantiomer with the desired optical purity.

14. Process according to claim 1, comprising the alternating and separate use of two different optically active organic acids, capable of forming diastereoisomeric salts with said R(-)-I and S(+)-I enantiomers, wherein said salts have different solubility in a given solvent and can be separated by crystallization.

15. Process according to claim 14, comprising:

(a) placing an R(-)-I and S(+)-I enantiomer mixture in contact, in a solvent, with a first optically active organic acid to form diastereoisomeric salts with said enantiomers, wherein said diastereoisomeric salts have different solubility in said

solvent and can be separated by crystallization, under conditions allowing the formation of a first precipitate;

(b) separating said first precipitate from the mother liquors, said mother liquors mainly containing one of said diastereoisomeric salts formed in step (a), and isolating the diastereoisomeric salt mixture enriched in the R(-)-I or S(+)-I enantiomer contained in said mother liquors;

(c) releasing the R(-)-I and S(+)-I enantiomers present in the diastereoisomeric salt mixture enriched in the R(-)-I or S(+)-I enantiomer, isolated from the mother liquors in step (b), by cleavage of said diastereoisomeric salts, generating a medium comprising a mixture of the R(-)-I or S(+)-I enantiomers enriched in one of said enantiomers, and said first optically active organic acid;

(d) removing said first optically active organic acid from the reaction medium;

(e) placing said enantiomer mixture enriched in R(-)-I or S(+)-I obtained in step (c), substantially free of said first optically active organic acid removed in step d), in contact, in a solvent, with a second optically active organic acid, different from the optically active organic acid used in step (a), to form the corresponding diastereoisomeric salts of said R(-)-I or S(+)-I enantiomers with said second optically active acid, wherein said diastereoisomeric salts have different solubility in said solvent and can be separated by crystallization, under conditions allowing the formation of a second precipitate and where the salt corresponding to the majority R(-)-I or S(+)-I enantiomer preferably precipitates in the reaction medium;

(f) separating said second precipitate formed in step (e) from the mother liquors, said second precipitate containing a mixture of the diastereoisomeric salts formed in step (e) enriched in the diastereoisomeric salt corresponding to the majority R(-)-I or S(+)-I enantiomer; and

(g) releasing the precipitated diastereoisomeric salts, enriched in the R(-)-I or S(+)-I enantiomer, to obtain the enantiomer mixture enriched in the R(-)-I or S(+)-I enantiomer.

16. Process according to claim 15, wherein said optically active organic acids used in steps (a) and (e) are the enantiomers of an optically active organic acid.

17. Process according to claim 16, wherein said optically active organic acids used in steps (a) and (e) are the D- and L- enantiomers of 10-camphorsulfonic acid, or the (+) or (-) enantiomers of N-(3,5-dinitrobenzoyl)-α-phenylglycine acid.

18. Process according to claim 15, wherein said second precipitate separated in step (f) is resuspended in a solvent, one time or more, to give rise to a new precipitate comprising a diastereoisomeric salt mixture enriched in one of the R(-)-I or S(+)-I enantiomers.

19. Process according to claim 15 for the separation of the R(-)-I enantiomer, wherein the first optically active acid is D-10-camphorsulfonic acid and the second optically active acid is L-10-camphorsulfonic acid [C(-)].

20. Process according to claim 15 for the separation of the R(-)-I enantiomer, comprising:

placing an R(-)-I and S(+)-I enantiomer mixture in contact with D-10-camphorsulfonic acid [C(+)], to form the I(+)C(+) and I(-)C(+) diastereoisomeric salts, in a solvent in which mainly the I(+)C(+) salt precipitates over the I(-)C(+) salt;

separating the mother liquors enriched in I(-)C(+) diastereoisomeric salt, isolating the salts contained therein and neutralizing them with a base to obtain an enantiomer mixture mainly containing the R(-)-I enantiomer, and removing the C(+) released after the neutralization of the mother liquors;

putting the enantiomer mixture enriched in R(-)-I in contact with the L-10-camphorsulfonic acid [C(-)], to form the I(-)C(-) and I(+)C(-) diastereoisomeric salts, in a solvent in which the I(-)C(-) salt mainly precipitates over the I(+)C(-) salt; and if so desired,

- neutralizing the precipitate obtained in the previous step with a base to obtain an enantiomer mixture mainly containing the R(-)-I enantiomer; or
- resuspending said precipitate in a solvent and maintaining the suspension at a temperature comprised between room temperature and the reflux temperature, for a time period comprised between 20 and 24 hours, generating a new precipitate; and if so desired,
  - neutralizing said new precipitate to mainly obtain the R(-)-I enantiomer; or

- resuspending said new precipitate, one time or more, until obtaining the R(-)-I enantiomer with the desired optical purity.

21. A diastereoisomeric salt selected from:

the diastereoisomeric salt of the R(-)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and D-10-camphorsulfonic acid;

the diastereoisomeric salt of the R(-)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and L-10-camphorsulfonic acid;

the diastereoisomeric salt of the S(+)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and D-10-camphorsulfonic acid;

the diastereoisomeric salt of the S(+)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and L-10-camphorsulfonic acid;

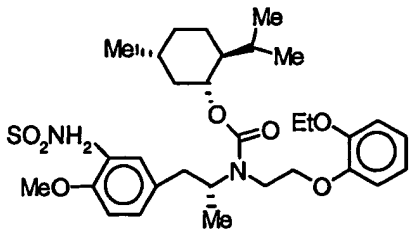
the diastereoisomeric salt of the R(-)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and (-)-N-(3,5-dinitrobenzoyl)-α-phenylglycine;

the diastereoisomeric salt of the R(-)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and (+)-N-(3,5-dinitrobenzoyl)-α-phenylglycine;

the diastereoisomeric salt of the S(+)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and (-)-N-(3,5-dinitrobenzoyl)-α-phenylglycine; and

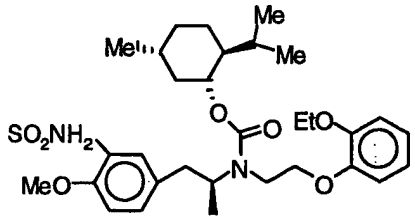
the diastereoisomeric salt of the S(+)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer and (+)-N-(3,5-dinitrobenzoyl)-α-phenylglycine.

22. A compound of formula II:



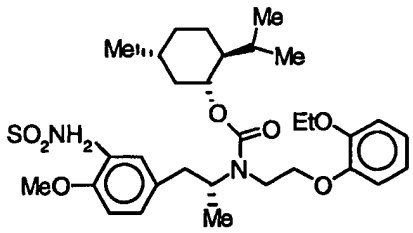
II

23. A compound of formula III:



III

24. A process for obtaining a diastereoisomeric carbamate of formula II or III,



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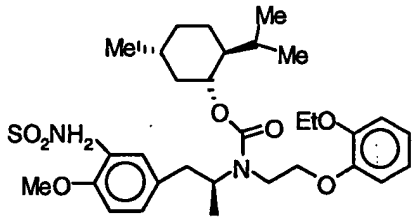
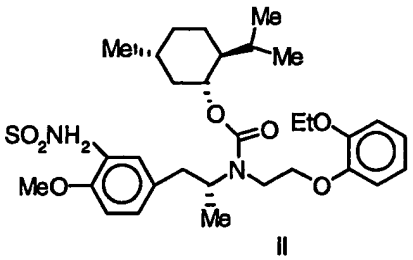


III

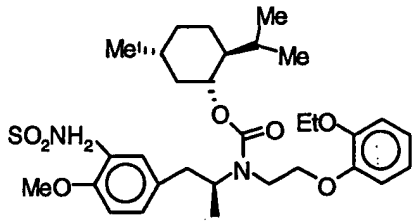
which comprises reacting the R(-)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer or the S(+)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino] propyl]-2-methoxybenzenesulfonamide enantiomer, or a mixture of both, with (-)-menthyl chloroformate, in a solvent, in the presence of a base.

25. A method for determining the degree of optical purity of a composition comprising the R(-)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide enantiomer, the S(+)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino] propyl]-2-methoxybenzenesulfonamide enantiomer, or mixtures of both enantiomers, comprising:

a) reacting a sample of said composition to be analyzed with (-)-menthyl chloroformate, to obtain the corresponding diastereoisomeric carbamate derivatives of formulas II and III; and



II



III

b) analyzing said diastereoisomeric carbamates of formulas II or III by means of high performance liquid chromatography (HPLC).

26. Method according to claim 25, wherein the reaction between the R(-)-I and/or S(+)-I enantiomers with (-)-menthyl chloroformate is carried out in a halogenated solvent, in the presence of a base.

27. Method according to claim 26, wherein the reaction between the R(-)-I and/or S(+)-I enantiomers with (-)-menthyl chloroformate is carried out in a halogenated solvent, in the presence of diisopropylethylamine.